

Commentary

Biosimilars: A Multidisciplinary Perspective



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ABSTRACT

A biosimilar is an officially regulated and approved copy of an originator biologic therapy. Improved affordability and consequent wider patient access compared with biologics are a significant appeal of biosimilars. Regulatory guidelines for biosimilar development and approval are rigorous and undergoing constant refinement. The process of licensing approval for all biosimilars requires demonstration of comparability in quality, efficacy, and safety between the biosimilar and reference (originator) product, which is undertaken in a stepwise procedure of nonclinical and clinical evaluation. The approval of >20 biosimilars in Europe in several drug classes, including the first monoclonal antibody biosimilar, bears testimony to the increasing regulatory acceptance of these agents. In contrast, the clinical application of biosimilars remains underrecognized by physicians across therapy areas. Therefore, this article aims to provide a comprehensive review of the biosimilar development process and to provide multidisciplinary guidance on the potential therapeutic utility of biosimilars in clinical practice. Specifically, experts discuss clinical developments in the introduction of biosimilars across the disciplines of gastroenterology, nephrology, oncology, and rheumatology, and from a payer perspective, and also highlight a common need for ongoing pharmacovigilance, robust head-to-head clinical studies, and real-world data to establish the long-term risk-benefit profile of biosimilars. In conclusion, significant potential exists for biosimilars to revolutionize biologic therapy by widening patient access across therapy areas. (*Clin Ther.* 2016;38:1238–1249) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: biosimilars, pharmacovigilance, safety, arthritis, Inflammatory Bowel Disease (IBD), Nephrology.

INTRODUCTION

The success of biologic therapies and impending patent expiry for many of these agents heralded the introduction of biologic similars (biosimilars), which have gained increasing acceptance since the first European Medicines Agency (EMA) approval of a somatropin biosimilar in 2006.¹ In early 2015, 20 biosimilars were approved in Europe ([Table I](#)), whereas a filgrastim biosimilar was approved by the US Food and Drug Administration (FDA) after a recommendation from the US Oncologic Drugs Advisory Committee.² Despite increasing acceptance from a regulatory perspective, biosimilars remain underrecognized by treating physicians.³ Therefore, the overarching aims of this article were to review the biosimilar development process and to provide guidance, from a multidisciplinary perspective, regarding the use of biosimilars in clinical practice.

WHAT IS A BIOSIMILAR?

Unlike small-molecule chemical agents, biologic therapies are proteins or peptides that have been developed using recombinant DNA technology in living systems and

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Table I. EMA-approved biosimilars.^{1,5,58,59,*}

INN (Molecule)	Product Name	Therapy Area	Approval Date
Epoetin alfa (HX575)	Abseamed	Chemotherapy-induced anemia	August 2007
	Epoetin alfa Hexal	Anemia associated with CKD [†]	
	Binocrit	Increasing yield during planned autologous blood transfusion	
Epoetin zeta (SB309)	Silapo	Chemotherapy-induced anemia	December 2007
	Retacrit	Anemia associated with CKD [‡]	
		Increasing yield during planned autologous blood transfusion	
Filgrastim (XM02, EP2006, PLD108)	Biogastrim	Cancer	September 2008
	Ratiogastrim	Hematopoietic stem-cell transplantation	
	Tevagrastrim	Neutropenia	
	Zarzio		February 2009
	Filgrastim Hexal		
	Filgrastim ratiopharm		September 2008
	Nivestim		Withdrawn April 2011
	Grastofil	Neutropenia	June 2010
	Accofil		October 2013
			September 2014
Follitropin alfa	Bemfola	Anovulation (IVF)	March 2014
Infliximab (CT-P13)	Inflectra	Ankylosing spondylitis	September 2013
	Remsima	Crohn's disease	
		Psoriatic arthritis	
		Psoriasis	
		Rheumatoid arthritis	
		Ulcerative colitis	
Somatropin	Omnitrope	Pituitary dwarfism	April 2006
		Prader-Willi syndrome	
		Turner syndrome	
		Turner syndrome	
	Valtropin	Pituitary dwarfism	April 2006
		Turner syndrome	Withdrawn May 2012
	Somatropin Biopartners	Growth hormone deficiency	August 2013

CKD = chronic kidney disease; EMA = European Medicines Agency; INN = international nonproprietary name; IVF = in vitro fertilization.

*Discussion of biosimilars targeted toward endocrinologic disorders is beyond the scope of this multidisciplinary article, which did not include an endocrinology specialist among the expert panel of authors.

[†]Licensed for intravenous administration.

[‡]Licensed for intravenous and subcutaneous administration.

extracted via complex purification techniques.^{1,4} Therefore, the structural and manufacturing complexity of biologic therapies and the requirement for proprietary knowledge preclude duplication, whereas the simpler

structures of small-molecule products and the ability to replicate the patented production process have facilitated development of generic versions, which are identical copies of the originator.⁵ Thus, biosimilar refers to a

product that is similar (but not identical) to the originator biologic therapy.⁴ In the United States and Canada, biosimilars are also known as follow-on biologics and subsequent entry biologics, respectively.⁶

DEVELOPMENT PROCESS FOR BIOSIMILARS

Due to the relatively recent introduction of biosimilars, the process by which these agents are tested and approved is continuously being updated and refined.⁴ Regulatory authorities including the European Medicines Agency (EMA), US Food and Drug Administration (FDA), and the World Health Organization have adopted unique measures for biosimilars, recognizing that the approval process for generic medicines cannot be applied to the licensing of biosimilars (Table II).^{4,7} Guidance from these organizations has been adopted as a reference for countries worldwide, including China, India, Latin Amer-

ica, and Russia.⁸ Key differences between countries relate to the choice of originator and extrapolation of indications.⁸ Regardless of the clinical indication, all biosimilars are required to undergo a comparability exercise in order to confirm a high degree of similarity with the reference product (originator) in terms of quality, biological activity, efficacy, and safety.^{9,10} Accordingly, the EMA, the first authority to establish a regulatory framework for biosimilars, has stipulated a process of approval that follows a stepwise procedure from detailed physicochemical and biological characterization toward nonclinical in vivo studies and clinical studies (Figure 1).^{9,10} The framework for biosimilars was an extension of the guidelines for comparability after manufacturing changes of originator biologics.¹¹ The EMA and other regulatory bodies have become highly experienced in comparability exercises, as these occur routinely for all biologics over time. The lessons learned

Table II. Biosimilar approval process of the EMA, FDA, and WHO.^{7,10,60}

	EMA	FDA	WHO
Classification of biosimilarity	"...a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product)."	"...that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."	"A biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product."
Essential requirements for confirmation of similarity with originator	Quality characteristics, biological activity, safety and efficacy	Safety, purity, and potency	Quality, safety, and efficacy
Approval system	Stepwise process to compare biosimilar with originator: 1. Comprehensive physicochemical and biological analyses 2. Nonclinical studies 3. Clinical studies		

EMA = European Medicines Agency; FDA = US Food and Drug Administration; WHO = World Health Organization.

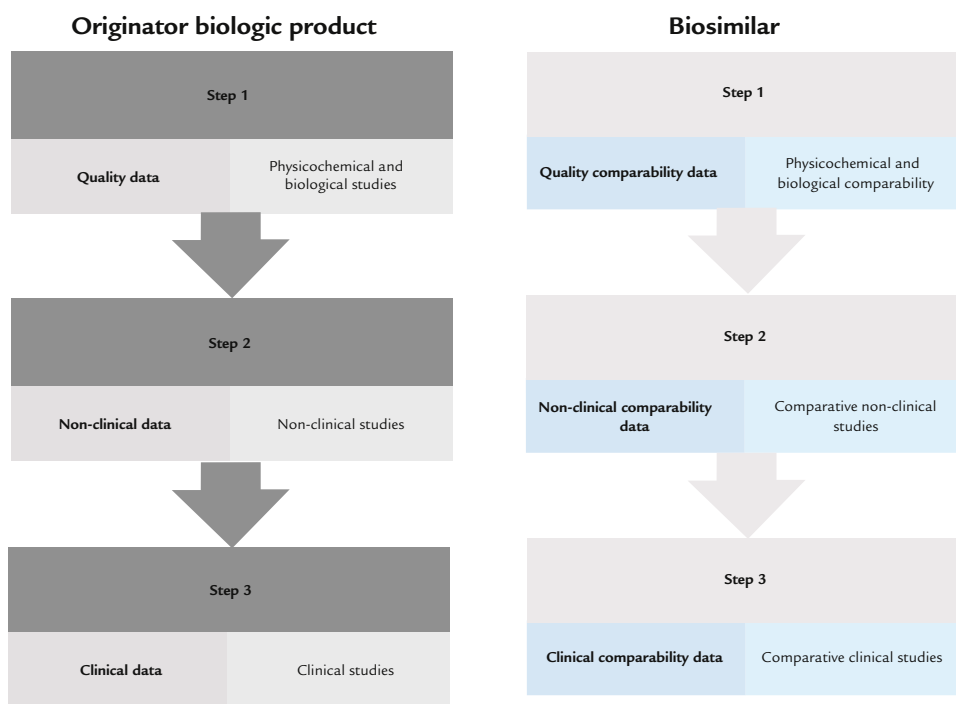


Figure 1. European Medicines Agency (EMA) approval processes for originator and biosimilar development.⁹ The approval process for originator products requires submission of quality, preclinical, and clinical data. The process of biosimilar approval developed by the EMA is based on demonstration of comparability to the originator product and, similar to the originator approval process, follows a stepwise procedure from detailed physicochemical and biological characterization to the undertaking of nonclinical in vivo studies and clinical studies. The extent and nature of the clinical evaluation depend on the level of evidence acquired in previous steps (in particular, the reliability of physicochemical, biological, and nonclinical in vitro data).^{8,9}

over the past 3 decades of managing the life cycle of biologics have been applied in the past 10 years to biosimilars. Thus, the biosimilar comparability exercise is not a new process invented for biosimilars, rather it is one that has been adapted from all biologics and now applied with great rigor to biosimilars.

Once EMA approval is granted, as with all biologics, manufacturers are also required to implement a rigorous pharmacovigilance program of their biosimilars within a risk-management plan to continuously monitor for and appropriately manage safety signals.⁹

NONCLINICAL AND CLINICAL DATA

Nonclinical (in vitro and in vivo bioanalytical, pharmacokinetic [PK], pharmacodynamic, and toxicological studies) and clinical data are required to show clinical/

therapeutic equivalence between the biosimilar and reference product.¹² To examine the nature of nonclinical and clinical evidence obtained, examples are drawn for biosimilars within the anti-tumor necrosis factor- α , erythropoiesis-stimulating agents (ESAs), and granulocyte colony-stimulating factor drug classes (Table I).^{12–14}

Nonclinical Testing

Extensive in vitro and in vivo investigations are undertaken before a biosimilar enters the next clinical evaluation step. Historically, comparability studies were first conducted and revealed similarity between the epoetin biosimilars HX575 and SB309 and the reference epoetin product (for intravenous [IV] and subcutaneous [SC] administration).^{15,16} As the first monoclonal antibody biosimilar approved in Europe, the infliximab biosimilar CT-P13 underwent

comprehensive nonclinical testing.¹³ Similarity of CT-P13 to reference infliximab was shown for molecular structure (including primary amino acid sequence, protein folding, and posttranslational modifications such as glycosylation), product stability and quality, and binding affinities for soluble monomeric and trimeric forms of tumor necrosis factor- α and transmembrane tumor necrosis factor- α .¹⁷ Additionally, the PK and toxicity profile of CT-P13 did not significantly differ from that of the reference product when both products were administered to rats at doses of 10 and 50 mg/kg.¹⁷

Clinical Efficacy

According to the EMA, the aims of clinical evaluation are to resolve slight differences potentially arising in previous steps of the development process and to confirm comparable clinical performance between the biosimilar and reference products.¹⁰ In aiming to show comparability, therapeutic equivalence is the generally accepted design, whereby a prespecified clinically accepted margin is appointed (and approved by the EMA) to establish whether differences exist between biosimilar and reference groups.¹² Clinical studies are actually confirmatory only with a focus on immunogenicity, PK equivalence, and therapeutic equivalence in a sensitive (previously approved) indication. Most often, these cannot be assessed effectively in nonclinical studies.

HX575 was deemed pharmacokinetically and pharmacodynamically bioequivalent to the reference epoetin based on a study in 80 healthy subjects that showed area under the curve (AUC) for epoetin concentration and area under the effect curves for hemoglobin (Hb) fell within established therapeutic bioequivalence 90% CI margins after a single IV bolus injection.¹⁸ Although a 10% reduction in HX575 exposure compared with the reference was noted, the authors concluded that both products were similarly efficacious at steady state.^{12,18} In clinical practice, the lower exposure could possibly translate to differences in clinical response if switching from the reference product to the biosimilar product.¹² Comparable bioavailability was noted for SC and IV administration of SB309 in 2 studies of healthy volunteers after post hoc analyses of the 90% CI margin for C_{max} and application of a correction factor to account for differences in protein content between SB309 and the reference epoetin.^{16,19,20} Clinical studies of HX575 and SB309 for correction of or maintenance

therapy for renal anemia have generally shown therapeutic equivalence of the 2 biosimilars versus the reference epoetin after IV administration.^{16,21–23}

European licensing approval for CT-P13 included 2 randomized, double-blind trials: a Phase I PK study in 250 patients with ankylosing spondylitis (PLANETAS [Program Evaluating the Autoimmune Disease Investigational Drug cT-p13 in AS Patients]) and a Phase III efficacy study in 606 patients with active rheumatoid arthritis (RA) despite methotrexate therapy (PLAN-ETRA [Program Evaluating the Autoimmune Disease Investigational Drug cT-p13 in RA Patients]).^{13,24,25} In PLANETAS, the primary end point was PK equivalence between CT-P13 at steady state and the reference infliximab, which was established if the 90% CI for the ratio of the mean for each agent was within the margin of 80% to 125%. Similarly, equivalent efficacy for CT-P13 and reference infliximab, as determined by the American College of Rheumatology 20% response at week 30, was the primary end point for PLAN-ETRA.²⁵ Results of both studies revealed geometric means approaching 100% for plasma exposure ([AUC] and C_{max}) in patients with ankylosing spondylitis and an American College of Rheumatology 20% treatment difference of 2% for patients with RA, thereby confirming the PK and clinical equivalence of CT-P13.^{24,25}

In other product classes, comparable efficacy of the biosimilar EP2006 and reference filgrastim in PK and pharmacodynamic studies of healthy adults as well as a single-arm, noncomparative study in breast cancer patients at high risk of chemotherapy-induced neutropenia formed the basis of its EMA approval in February 2009.⁴

Safety

EMA guidelines specify that the safety of a biosimilar is assessed using parameters that are identical to those used to evaluate the reference product and in a large enough patient population to compare adverse event frequencies.²⁶ In general, clinical studies of biosimilars have demonstrated adverse event profiles that are comparable to the reference product class.^{13,14,27} As for originator biologics, there are additional safety implications, most notably related to immunogenicity.⁴ Risk of immunogenicity is a concern with any biologic therapy, with the potential for small molecular variations to translate to clinically significant immunogenicity differences

manifesting as acute anaphylaxis, serum sickness, or antibody generation.^{26,28} Preclinical safety assessments and risk mitigation strategies are aimed toward characterizing biologics and therefore minimizing such risks before clinical testing.^{28,29}

Although cases of immunogenicity may not always produce clinical consequences, the generation of antibodies could compromise treatment efficacy and/or trigger systemic immune reactions.¹² Pure red cell aplasia (PRCA) is a serious, albeit rare, immunogenic adverse event associated with epoetin products and occurred at a significantly higher incidence after a formulation and packaging change in the epoetin alfa reference biologic EPREX in 1998.³⁰ It is important to note that the lessons learned from the emergence of PRCA with the originator product were incorporated into the biosimilar guidelines and that since their approval in 2007, there is no available evidence of an increased risk of PRCA associated with the use of an approved biosimilar epoetin in a regulated market in the postmarketing setting.

Although existing pharmacovigilance data implied that the background rate for PRCA for epoetin biologics was approximately 1 in 100,000 patient-years, the reporting of a case of PRCA confirmed by neutralizing anti-epoetin antibodies after SC administration in the HX575 treatment group, as well as a second suspected case of PRCA, led to the early termination of SWEEP (Study to Evaluate the Efficacy, Safety and Immunogenicity of Subcutaneous HX575 in the Treatment of Anemia Associated With Chronic Kidney Disease).^{12,31} The SC route of administration was thus not approved by the EMA, and HX575 remains IV administration only. This is evidence demonstrating that the rigorous processes of biosimilar testing are working reliably. Nevertheless, results from SWEEP highlight the need for ongoing characterization of emerging safety issues related to biosimilar use and underscore the fundamental importance of continued pharmacovigilance.¹² Indeed, risk-management plans for biosimilar epoetins include additional postmarketing surveillance studies to address rare immunogenic events such as PRCA.⁴

In trials of CT-P13, the development of antidrug antibodies in CT-P13-treated patients was not found to differ markedly from patients initially given reference infliximab or those who switched from the reference product to CT-P13 at the end of the first year of a 2-year extension study.^{13,24,25} Guidance has

been issued to prohibit automatic substitution of biosimilars, with prescribing decisions clearly assigned to the physician.^{4,5}

Other aspects of biosimilar development and utilization that have implications for safety are interchangeability, which may allow for automatic substitution, and switching, a decision made by a physician to substitute a biosimilar for its reference product. Details of these concepts have been comprehensively discussed elsewhere.^{5,32} In the United States, based on guidance from the FDA, for a biosimilar to be considered interchangeable with its reference product, the agent must demonstrate a capability of being switched without incurring significant safety risks (as well as reduced efficacy) at an individual patient level. Additionally, for a product administered more than once, safety and reduced efficacy risks of switching must not be greater than with repeated use of the reference product. Only with an FDA-approved interchangeability designation would automatic substitution be allowed at the pharmacy.¹ In Europe, the EMA does not provide a definition of interchangeability, but rather leaves the decision regarding automatic substitution to the European Union member states. For the most part in the European Union, country-specific laws have been enacted that do not allow automatic substitution of biosimilars for their reference biologics.^{4,5}

Despite a lack of consensus on the evaluation of interchangeability, switching was assessed in an open-label 48-week extension of a Phase III trial of CT-P13, and it was concluded that there were generally consistent safety profiles between the CT-P13 group and those who switched from the reference infliximab to CT-P13 after 54 weeks of treatment.¹³ After switching from intravenously administered epoetin alfa to IV SB309 in a head-to-head crossover trial, the mean weekly doses of epoetin zeta and the reference epoetin were within the established equivalence margin (92.68 and 92.58 IU/kg/wk for epoetin zeta and the reference epoetin alfa, respectively). Similarly, mean Hb levels were within the established margins (11.35 and 11.54 g/dL for epoetin zeta and reference epoetin alfa, respectively), whereas minor nominal dose adjustments to maintain steady Hb levels were seen between treatment periods.²³ Although potential concerns exist regarding switching between an originator and a biosimilar, a 2012 review found no evidence of any relevant safety issues from clinical trial or postmarketing surveillance data.³³

Extrapolation of Data

After the rigorous comparability exercise comprising both nonclinical and confirmatory clinical studies, on the basis of appropriate nonclinical scientific justification, a given biosimilar may be approved for other indications for which the originator product is licensed without the necessity for clinical data on those indications (referred to as *indication extrapolation*).^{26,34} Extrapolation may benefit from a common mechanism of action across indications.³⁴ For example, epoetin has a single target binding site, whereas monoclonal antibodies have binding regions that participate in numerous biological activities.³⁴ However, it is important to consider that differences in efficacy and safety risk may exist between indications.^{26,34} Thus, despite potential benefits of indication extrapolation (eg, cost savings and wider patient access), a cautious approach to selection of patient populations may be warranted, especially where the mechanism of action may differ.^{26,35}

There was extensive bioanalytic assessment of all known mechanisms of action for Crohn's disease and ulcerative colitis, which showed in relevant nonclinical models that CT-P13 and the originator infliximab did not differ. Based on the totality of evidence (highly comparable physicochemical and functional characteristics, equivalent pharmacokinetics and pharmacodynamics, comparable immunogenicity, therapeutic equivalence in a sensitive indication, and nonclinical interrogation of all known mechanisms of action in the inflammatory bowel disease indications), the EMA granted extrapolation to all the indications approved for reference infliximab. As a result, in the case of biosimilar infliximab, a significant cost reduction enables meaningfully greater access to a critical biologic therapy in patients with inflammatory bowel disease (IBD), potentially earlier in the course of their disease within the context of international recommendations.

Pharmaeconomic Value of Biosimilars

A fundamental aim in developing biosimilars is to improve patient outcomes by offering access to biologics with improved affordability.⁵ Bearing in mind that the primary purpose of biosimilar clinical study programs is to confirm comparable efficacy and safety in a sensitive patient population, the availability of such data has nevertheless enabled the development of cost models to ascertain the feasibility of potential cost

savings with biosimilars compared with their reference products. Two budget impact analyses have estimated that the use of CT-P13 for RA treatment in selected countries in Central and Eastern Europe (Bulgaria, Czech Republic, Hungary, Poland, Romania, and Slovakia or Ireland) may generate cost benefits that are 20% to 25% lower compared with the reference infliximab. The potential for cost savings is particularly pertinent for impoverished European countries where patient access to biologics is curtailed to a greater extent than in higher income countries.³⁶

MULTIDISCIPLINARY EXPERT PERSPECTIVES

Gastroenterology

The recent approval of infliximab biosimilars for IBD has prompted significant debate in the field of gastroenterology.^{6,37} Physicians have been generally unaware of the innovative licensing approach on which the approval of biosimilars is based.³ Misunderstanding among gastroenterologists may arise, in particular, from a heavy reliance on robust disease-specific clinical trial data (eg, for Crohn's disease and UC) to gauge clinical validity as is a prerequisite for originator therapies, but may be superfluous, time-consuming, and costly in the case of biosimilars.³⁷ Therefore, gastroenterologists should be aware that there is a crucial distinction between the evaluation of originators and biosimilars in that preclinical research involving physicochemical, PK, and pharmacodynamic analyses drive the approval process for biosimilars, with existing or new clinical trials providing important supporting data. The licensing of CT-P13 is a pertinent example of this process, which encompassed extensive physicochemical characterization based on batch-to-batch analysis, as well as nonclinical and clinical studies and mechanism of action studies to confirm similarity with the originator infliximab.³⁸ This approach will expedite the introduction of biosimilars in real-world practice.

From the perspective of the Czech Republic, the rapid and robust reduction (30%–40%) in costs associated with biosimilars has facilitated earlier initiation of biologic therapy in those patients with IBD on treatment waiting lists, with 1000 more entering treatment in 2014 compared with the previous year. Emerging results from prospective observational studies, including interim data from a Hungarian nationwide cohort, support the short-term

clinical efficacy and safety of CT-P13 in patients with IBD, including those who switched from the originator infliximab.^{39,40} Although such results are promising, implementation of national registries of IBD patients on biologic therapy; prospective, long-term real-world data on clinical efficacy and safety; and better dissemination of the approval process are, among others, essential factors that will need to be addressed if biosimilars are to gain widespread acceptance in gastroenterology.

Nephrology

ESA markets for treatment of chronic kidney disease-associated anemia have proven to be highly country-specific, and even across EU countries, the penetration rate of biosimilar epoetins varies significantly.⁴¹ The still unsatisfying acceptance of biosimilar epoetins is multifactorial, often due to a persistent lack of information and expertise in the field of biological agents. A lack of availability of biosimilar advocacy and policies, together with the sometimes confusing nomenclature, promotes further uncertainties.

Despite such studies as the pan-European, prospective Monitor-CKD5 (Multi-level Evaluation of Anaemia Treatment, Outcomes, and Determinants in Chronic Kidney Disease Stage 5) study of HX575,⁴² additional large-sample, long-term observational studies are urgently needed. When reviewing the ESA class of biological products, a recent systematic analysis of adults with chronic kidney disease suggested that the currently available clinical evidence was markedly less than that of the proprietary ESAs.⁴³ The marketing withdrawal of peginesatide, a long-acting originator ESA, that was recalled in February 2013 after reports of severe hypersensitivity reactions in dialysis patients who received a first dose, is a warning example that strict postmarketing surveillance is important.⁴⁴ In addition, nephrologists are encouraged to carefully observe developments worldwide including threshold countries, where often extensive practical experience with biosimilar ESAs exists.³¹ Long-term postmarketing real-world data demonstrating clinical effectiveness, safety, and finally cost savings are required to complete the success story of biosimilar ESAs in the field of nephrology.

Oncology

Use of biosimilars in oncology to date has been largely confined to supportive care therapy such

as filgrastim and ESA biosimilars, which, on the whole, have been shown to be comparable in efficacy and safety to their originators.⁴⁵ The clinical success of these supportive care agents in oncology invites the development of biosimilars for curative therapy.

Institutions welcome the potential for significant reduction in costs with biosimilars as well as oncologists, many of whom report that drug costs feature in their clinical decisions.⁴⁶ Cost-effectiveness and establishment of best practice and ongoing postmarketing surveillance have been researched in the routine clinical management of the oncology patient. Large observational studies (MONITOR-GCSF [Multi-level Evaluation of Chemotherapy-induced Febrile Neutropenia Prophylaxis, Outcome, and Determinants with Granulocyte-colony Stimulating Factor], NEXT, and ORHEO [Epoetin Alfa Biosimilar in the Management of Chemotherapy-Induced Symptomatic Anaemia in Haematology and Oncology]) across European countries report long-term efficacy and safety of the biosimilars filgrastim and epoetin for febrile neutropenia or chemotherapy-induced anemia, respectively, in real-world patients with cancer.^{47,48} The cost reductions associated with biosimilar granulocyte colony-stimulating factor have resulted in an increase in access in most European markets (ranging from 2% in Belgium to an almost 100% share of the accessible market in Croatia, Czech Republic, Hungary, and Romania)⁴⁹; this may be a demonstration of the “real value” of biosimilars.

Rheumatology

The infliximab biosimilar has already been introduced in some countries for rheumatic conditions. In addition to ongoing studies on other anti-tumor necrosis factor- α biosimilars (eg, adalimumab and etanercept), several rituximab biosimilars are in advanced stages of development, and some are currently undergoing evaluation in clinical trials of patients with RA.⁵⁰ Results from these studies, if positive, will contribute to existing clinical data for infliximab biosimilars in RA.⁵¹ There remain, however, pertinent and valid challenges to the introduction of biosimilars in rheumatology, not least is the need for additional disease-specific clinical trials and postmarketing surveillance data.⁵²

As for other areas of medicine, rheumatologists' awareness of biosimilars is lacking (when compared,

for example, with other biologic therapies), particularly among those physicians with less clinical experience.⁵³ Encouragingly, rheumatology experts and organizations worldwide have taken a collective stance to inform and guide physicians on the clinical utility of biosimilars in rheumatic diseases.^{52,54} The success of biosimilars, nevertheless, will lie with practicing rheumatologists and their trust in the evidence base for biosimilars in rheumatology.

Payer

Together with the clinical benefits, the potential for significant cost savings and consequent greater patient accessibility renders biosimilars an attractive proposition for payers.⁵⁵ Possible cost advantages conferred by competitive pricing (eg, as seen for generics) may be tempered by such factors as the ability to automatically substitute products.⁵⁵

To date, evidence generally supports the cost benefits of biosimilars.^{49,56} As part of the first scheme operated by the London Procurement Programme in the United Kingdom, a process was implemented to rationalize the use of erythropoietin for chronic kidney disease patients in South London in 2006 with collaboration from renal centers and Primary Care trusts (David Stead, personal communication). Specifically, agreement was reached to repatriate a number of patients to 1 of 4 centers where rational drug use was initiated based on a tender that clearly indicated

which would/should be first-line for new patients and those who were switching treatment. This produced a cost saving of several million GBP per year (David Stead, personal communication) and has since been replicated in other UK regions. In implementing such a process for a biosimilar, there are important considerations to take into account: assessing the current market (who is prescribing the drug [general practitioner or hospital]); whether it is possible to rationalize the range of products used; how to gain the best price (usually in hospital) and whether health care trusts can meet the potentially higher workload; and ensuring a collaborative approach from all parties concerned. Thus, with resolution of key issues such as the lack of real-world cost and best practice data, the prospect of cost advantages and greater patient access works in favor of biosimilars from a payer perspective.

DISCUSSION AND CONCLUSIONS

Regulatory authorities have implemented guidelines for the development and approval of biosimilars for clinical use, but physicians have been largely unaware of the nature of these processes.³ Physicians also need to be aware of the monitoring routinely performed by regulatory agencies to assess manufacturing changes in biologics in order to ensure that such changes do not lead to changes in the originator molecule.⁵⁷ The

Table III. Issues in biosimilar development process and clinical practice.

Process	Issue	Potential Solution
Substitution ^{4,12} (of originator for biosimilar or between biosimilars)	Unintentional or automatic substitution by pharmacists	Regulatory measures to define automatic substitution policies
Switching/ interchangeability ^{5,58,*}	Safety and efficacy effects of switching or alternating to and from biosimilars and their reference products	Studies investigating switching and/or alternating between existing biologics
Pharmacovigilance ¹²	Confusion in naming for AE drug reports	Appropriate measures to identify product brand name and batch number Regulatory bodies adopt and approve risk-management plans to include specifically focused postmarketing studies

AE = adverse event; INN = international nonproprietary name.

reduced clinical data requirement for biosimilars compared with that stipulated for originators may have given physicians cause for concern with respect to the reliability of the evidence supporting the approval of biosimilars.⁵ As summarized in [Table III](#), there remain gaps in the process that clinicians should be aware of in order to effectively and safely prescribe biosimilars, although the continuously evolving nature of the biosimilar approval process will undoubtedly resolve these issues in time. Additionally, it must be noted that all biologics must manage nonidenticality, not just biosimilars. This includes microheterogeneity and batch-to-batch variability and potentially intended and unintended drift due to manufacturing changes over time. Because of the inherent variability of biologic systems, biologics cannot be identical to themselves. Therefore, the biosimilar must replicate the variability of the biologic being copied. The rigorous nature of the biosimilar development process reviewed here offers a safeguard to clinicians who may have experienced some uncertainty regarding the use of biosimilars in their clinical practice.

In this article, multidisciplinary experts spanning the fields of gastroenterology, nephrology, oncology, and rheumatology and from a payer perspective highlight a real potential for biosimilars to revolutionize biologic therapy by increasing access to a wider patient population across disciplines, but only with appropriate implementation of postmarketing strategies to monitor risk-benefit profiles over the long term.

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Dr. Scotte has received honoraria or consulting fees from Hospira, Teva, Sandoz, Roche, Pierre Fabre Oncology, and AMGEN. Dr. Khraishi has received honoraria or consulting fees from Amgen Canada, Abbvie, Janssen, Pfizer, and Roche. The other authors have indicated that they have no conflicts of interest regarding the content of this article.

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